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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,283	08/11/2000	RICHARD KROCZEK	50125/011001	7620

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EXAMINER	
ROARK, JESSICA H	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/509,283	Applicant(s) KROCZEK, RICHARD	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/15/00, 5/25/01, 8/7/01, 12/13/01 and 4/22/02*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-76,78-83,85,86 and 88-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-76,78-83,85,86 and 88-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 August 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5, 5, 5, 9, 14, 16 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendments, filed 8/15/00, 5/25/01, 8/7/01, 12/13/01 and 4/22/02 (Paper Nos. 6, 10, 13, 20 and 23), are acknowledged.

Claims 71-100 have been added.
Claims 71, 76, 78, 83, 85-86, 88-97 have been amended.
Claims 1-70 and 77, 84 and 87 have been canceled.
Claims 71-76, 78-83, 85-86 and 88-100 *are pending.*

2. Applicant's election of Group III in Paper No. 10 is acknowledged. Applicant's cancellation of the previously pending claims has however rendered the restriction requirement moot.

Claims 71-76, 78-83, 85-86 and 88-100 *are under consideration in the instant application.*

3. Sequence compliance: Applicant's amendment introducing a substitute paper copy of the sequence listing, substitute CRF, and Statement that the paper copy and disk are the same, filed 4/22/02 are acknowledged.

It is noted that SEQ ID NO:2 in the paper copy and CRF was corrected in the response filed 12/13/01 such that SEQ ID NO:2 is now the same as that disclosed in the originally filed paper copy of SEQ ID NO:2, as encoded by SEQ ID NO:1, and as shown in Figure 15.

The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. Priority: Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.
However, English translations for foreign priority documents DE 197 41 929.1 and DE 198 21 060.4 have not been provided. Although certain aspects of the instantly recited claims do appear to be supported in the foreign priority documents, it is unclear whether the foreign priority documents provide adequate written description for the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112, first paragraph.

5. The Kroczek Declaration filed on 5/25/01 under 37 CFR 1.131 is acknowledged, but does not appear to be relevant to the rejections set forth below.

6. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the copy of form PTO-948 attached, previously provided as part of Paper No. 21.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

*Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.*

7. Applicant's IDSs, filed 8/15/00, 9/1/00, 5/25/01, 8/9/01 and 10/12/01 (Paper Nos. 5, 5.5, 9, 14 and 16), are acknowledged.

Dates are need for both Tamatani and Tezuka GenSeq Database submission, W75956 and V53199.
The Chambers and Allison (Cur. Opin. Immunol. 1997; 9:396-404) and Lucas et al. (J. Immunol. 1995; 154:5756-5768) references filed on the IDS submitted 9/1/00 have been lined thru since these references also appear on the IDS filed 8/15/00.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 71-75, 78-83, 85-86, 88-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The recitation of "costimulates" in claims 71-75, 78-82, 85 and 89-96 is ambiguous because the metes and bounds of this term are unclear. The specification discloses on pages 4-5 that "costimulation" affects multiple T cell functions, but not necessarily in the same way. For example, CD28 costimulation of T cells includes production of the cytokine IL-2, whereas costimulation via the 8F4 polypeptide does not. Thus a recitation of "costimulates" without the inclusion of a particular testable "costimulating activity", such as in vitro stimulation of T cell proliferation, fails to establish the metes and bounds of the claim.

It is suggested that Applicant amend the claims to indicate that the monoclonal antibody, in conjunction with anti-CD3 monoclonal antibody OKT3, costimulates proliferation of human T lymphocytes, as supported on page 5 at lines 17-21 and Example 4 on pages 15-16.

B) Claims 78-83 and 93-96 lack proper antecedent basis for the recitation of the phrase "wherein the monoclonal antibody" in the next to last line of claims 78 and 83 because the preamble recites "A hybridoma". In addition, the claim as written is ambiguous as to whether the monoclonal antibody of the "wherein" clause refers to the monoclonal antibody produced by the hybridoma of the preamble, or the monoclonal antibody deposited with the DSMZ.

It is suggested that Applicant amend the "wherein" clause to recite "wherein the hybridoma produces a monoclonal antibody that" to clearly indicate that each of the recited properties is shared by all antibodies produced by the hybridoma of the preamble.

C) Claims 85-86 lack proper antecedent basis for the recitation of the phrase "wherein the monoclonal antibody" in the next to last line of each claim because the preamble recites "A pharmaceutical composition". In addition, the claim as written is ambiguous as to whether the monoclonal antibody of the "wherein" clause refers to the monoclonal antibody of the pharmaceutical composition of the preamble, or the monoclonal antibody deposited with the DSMZ.

It is suggested that Applicant amend the "wherein" clause to recite "wherein the pharmaceutical composition comprises a monoclonal antibody that" to clearly indicate that each of the recited properties is shared by all antibodies produced by the hybridoma of the preamble.

D) Claims 88 and 97-98 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: those steps which result in the selection of a hybridoma producing an antibody that recognizes the 8F4 polypeptide. The majority of hybridomas from an immunized mouse do not produce antibodies to the antigen of interest.

It is suggested that Applicant amend the claim to include steps such as those disclosed on page 7 of the specification at lines 1-21, particular the step of identifying the desired specificity.

E) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. It is apparent that the OKT3 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent vector. See 37 CFR 1.801-1.809.

However, it is noted that the OKT3 antibody is produced by the hybridoma CRL 8001, which is publicly available from ATCC as shown by the attached entry for CRL 8001 (ATCC Cell Lines and Hybridomas, page 393, 8th edition, 1994 American Type Culture Collection, current address 10801 University Boulevard, Manassas, VA 20110-2209); therefore the enablement requirement with respect to the OKT3 antibody appears to be satisfied.

13. Claims 71-76, 78-83, 85-86, 88-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the 8F4 antibody and DSM ACC2539 hybridoma producing it are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines which produce these antibodies. See 37 CFR 1.801-1.809.

It is noted that Applicant has indicated in the Response filed 4/22/02 that the DSM ACC2539 hybridoma producing the 8F4 antibody was deposited with the DSMZ on 4/9/02 under the terms of the Budapest Treaty and assured in that Response that all restrictions will be irrevocably removed upon granting of a patent.

However, Applicant still must promptly submit a verified statement from a person in a position to corroborate the fact, *that the biological material which is deposited is the biological material specifically identified in the application as filed*, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified (see MPEP 1.804(b) and MPEP 2406).

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

In addition, Applicant is reminded to amend the specification to disclose the accession number of the deposit, date of deposit, and the complete name and address of the depository.

14. Claims 71-76, 78-83, 85-86 and 88-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a monoclonal antibody to the 8F4 polypeptide, pharmaceutical compositions thereof and hybridomas producing, as well as for a monoclonal antibody that inhibits a testable activity of the 8F4 polypeptide, does not reasonably provide enablement for a monoclonal antibody to a "fragment" of the 8F4 polypeptide or a monoclonal antibody that inhibits a "biological activity" of the 8F4 polypeptide, nor for a pharmaceutical composition comprising, hybridoma producing, or methods of producing said monoclonal antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to how to make and use a monoclonal antibody specific for a fragment of the 8F4 polypeptide, or a monoclonal antibody that inhibits any "biological activity" of the 8F4 polypeptide.

The scope of the instant claims encompasses a monoclonal antibody that recognizes *any* fragment of the 8F4 polypeptide, including a single amino acid. No working examples are provided of an antibody to a fragment of the 8F4 polypeptide. In addition, the specification does not appear to provide sufficient guidance as to which fragments of the 8F4 polypeptide encompass an antibody epitope. Regenmortel (METHODS: A companion to Methods in Enzymology 1996; 9:465-472) teaches that even when guidance is given in the form of various computer algorithms (which is not provided in the instant specification), the success rate of antigen prediction is low, because the predictions concern only continuous epitopes (e.g., page 467, last paragraph). Further, the skilled artisan was well aware that monoclonal antibodies produced to fragments of the 8F4 polypeptide would have structural and functional properties that were highly diverse compared to antibodies produced by immunizing with the 8F4 polypeptide. Without guidance as to which fragments of the 8F4 polypeptide to use as an immunogen, it would require undue experimentation of the skilled artisan to make the plethora of fragments contained within the 8F4 polypeptide and determine which of these fragments could be recognized by an antibody that costimulates human T cells in conjunction with OKT3, or that inhibits any other "biological activity" of the 8F4 polypeptide.

Further, claims such as claim 76 encompass antibodies which inhibit *any* "biological activity" of the 8F4 polypeptide. However, in the absence of some specific testable function, it would require undue experimentation of the skilled artisan to make and use antibodies which inhibit any "biological activity" of the 8F4 polypeptide. Similarly, the state of the art recognized that for any given polypeptide, most of the possible "fragments" of the polypeptide would not share the "biological activity" of the intact polypeptide. Without sufficient guidance as to which *fragments* of the 8F4 polypeptide had any particular "biological activity", the skilled artisan would not know how to make an antibody to a *fragment* of the 8F4 polypeptide that could inhibit any given "biological activity", even were the "biological activity" limited to a testable activity.

The skilled artisan would also require further guidance as to which particular "biological activity" of the 8F4 polypeptide was to be inhibited before the skilled artisan would be able to either make antibodies with this functional property, or use monoclonal antibodies in a pharmaceutical composition. Similarly, it would be highly unpredictable that an antibody to a fragment of the 8F4 polypeptide which did not share the functional properties of the 8F4 polypeptide, such as stimulating proliferation of activated human T cells in vitro, would have the same functional activity as antibodies to the full length 8F4 polypeptide; therefore making it highly unpredictable that such antibodies could be used in a pharmaceutical composition.

Finally, since the skilled artisan has not been provided sufficient guidance as to how to make and use antibodies to fragments of the 8F4 polypeptide or antibodies that inhibit any biological activity; the skilled artisan also would not know how to make and use hybridomas producing such monoclonal antibodies.

Thus the scope of the claimed antibodies is not commensurate with the enablement provided by the disclosure with regard to the large number of polypeptides fragments broadly encompassed by the instant claims to which the instant antibodies are specific, or the diverse biological activities inhibited by the antibody. Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed antibodies in a manner reasonably correlated with the scope of the claims broadly including antibodies to *any* fragment of the 8F4 polypeptide and/or able to inhibit *any* biological activity. In the absence of such guidance for these monoclonal antibodies, there is also insufficient guidance as to how to make and use hybridomas producing said antibodies and pharmaceutical compositions comprising. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without sufficient guidance, it is unpredictable as to which of the antibodies specific for fragments of the 8F4 polypeptide would also be specific for the enabled embodiment of the full length 8F4 polypeptide. Similarly, without sufficient guidance as to which biological activities were to be inhibited by the antibodies, it would be unpredictable that the skilled artisan could make and use an antibody able to inhibit *any particular* biological activity. Consequently, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

15. It is noted that Redoglia et al. (Eur. J. Immunol. November 1996; 26:2781-2789, IDS #AD) teach the C398.4A antibody, which recognizes a mouse protein known as "H4". As evidenced by Buonfiglio et al. (Eur. J. Immunol. December 2000; 30:3463-3467, IDS #AC) and Mages et al. (Eur. J. Immunol. April 2000; 30:1040-1047), the C398.4A antibody also recognizes the human ICOS polypeptide, which is the same polypeptide as the instant 8F4/SEQ ID NO:2.

However, Buonfiglio et al. also teach that the C398.4A antibody in combination with the anti-human CD3 antibody OKT3, does not co-stimulate proliferation of human T cells.

Thus the instant claims do not appear to be anticipated by the teachings of Redoglia et al.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
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July 10, 2002

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7/10/02